Molecular taxonomy in Bladder Cancer

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Disclosures

• Advisory Board member for AstraZeneca and MSD
Timeline of transcriptomic classifications in bladder cancer
Chapel Hill
Damrauer et al

MD Anderson
Choi et al

CIT
Rebouissou et al

TCGA (1st)
Consortium

NMIBC
Hedegaard et al

Lund (2nd)
Sjödahl et al

Neoadj. Chemo.
Seiler et al

TCGA (2nd)
Robertson et al

Consensus taxonomy?
Molecular differentiation: two main groups
the “luminal / basal” paradigm

Identification of Distinct Basal and Luminal Subtypes of Muscle-Invasive Bladder Cancer with Different Sensitivities to Frontline Chemotherapy

Intrinsic subtypes of high-grade bladder cancer reflect the hallmarks of breast cancer biology

KRT14, KRT5/6, FOXA1, GATA3, KRT20

luminal ~ urothelial differentiation
Muscle invasive bladder cancer taxonomies
Multiple names...Different definitions and numbers of molecular subtypes...

Which level of subclassification (granularity) in muscle invasive bladder cancer is relevant
- At biological level ?
- At clinical level ?
Non muscle invasive bladder cancer taxonomies

• Only few molecular taxonomies were described so far:
  o Lund taxonomy gathering muscle and non-muscle invasive bladder cancer (Sjödhal, 2012)
  o Aarhus one focusing only on non-muscle invasive bladder cancer (Hedegaard, 2016)

• Further work are required to determine at which extent the same molecular entities occur across the different tumor stages, in muscle and non muscle invasive bladder cancer
Chapel Hill
Baylor
MDA
TCGA
Lund
CIT

14 MIBC datasets
(1312 mRNA profiles)

mRNA predictors for the 6 subtyping systems

Luminal papillary consensus subtype?

ChapelHill.subtype
Baylor.subtype
MDA.subtype
TCGA2017.subtype
Lund2017.subtype
CIT.subtype

- Luminal
- Basal
- Differentiated
- Basal
- Luminal
- p53–like
- Basal_squamous
- Neuronal
- Luminal_papillary

- UroA–Prog
- UroC
- Uro–Inf
- UroB
- GU
- Ba/Sq–Inf
- Ba/Sq
- Mes–like
- Sc/NE–like
- GU–Inf

Basal-like consensus subtype?

Neuroendocrine-like, consensus subtype?
Meeting Report

Bladder Cancer Molecular Taxonomy: Summary from a Consensus Meeting

• 1st meeting march 2015
• + 2 meetings 2017/ 2018

To build a consensus from distinct classifications
(A de Reynies, A Kamoun, F Radvanyi, Paris)

As for “The consensus molecular subtypes of colorectal cancer, Guinney, Nature Med 2015”
To be validated and accepted!
Molecular subtypes are associated with overall survival

Outcome after neoadjuvant chemotherapy might be associated with molecular subtypes (retrospective analysis to be confirmed)

Aurelie Kamoun, in progress
Basal / squamous like subtype (35%)

- Associated with squamous divergence (50%) of cases
- Basal keratin expression
- Poor prognosis but seems to be improved after neoadjuvant chemotherapy
- EGFR pathway activated
- Rich immune microenvironment (lymphocytic and myeloid)
Luminal – papillary subtype (23%)

- Associated with papillary pattern in surface
- Most FGFR3 mutations or translocations (80%) are observed within this subtype and 50% luminal papillary tumors are FGFR3 mutated or translocated
- Often low immune infiltrate
- Better prognosis than other subtypes
Neuronal / neuroendocrine like tumours (6%)

A large fraction not identified as neuroendocrine carcinoma at histological level? Further characterization is required

TCGA 2017, Robertson
Non “luminal papillary” luminal tumours (22%) : 1 or 2 groups ? to be further characterized

Infiltrated tumours (14%) : an intrinsic entity ?
Need to develop and validate tools (immunohistochemical panel and/or molecular signatures) that could be used in clinical practice to identify these molecular subtypes, refine histological diagnosis and help treatment decisions.
Limited panel?

CK 5/6, CK 14, GATA3, FOXA1 (Lerner, 2016)

- To identify basal / squamous like tumours, but sensitivity can be limited (70%, personal experience)

- Thresholds (intensity? %?)

- Not able to discriminate among luminal subtypes
Extensive panel?

- The Lund approach (FGFR3, CCND1, RB, p16, CK5, CK14, VIM, EB2, E-Cadh, EPCAM, TUBB2B)

- IHC (tumor cell phenotype) and molecular markers (tumor cells and stroma) can be complementary

Sjödahl, J Pathol 2017; Sjödahl, Methods Mol Biol 2018; Mazourka, Sci Rep 2018
Future?

• Mandatory to standardize and validate thresholds on the basis of consensual definition for each entity.

• To determine how the histological variants of invasive urothelial carcinoma are classified at molecular level.

• To take into account the spatial and temporal intra-tumoural heterogeneity that can be encountered, spontaneously or after therapeutic intervention.


○ Hovelson DH et al. Targeted DNA and RNA Sequencing of Paired Urothelial and Squamous Bladder Cancers Reveals Discordant Genomic and Transcriptomic Events and Unique Therapeutic Implications. Eur Urol. 2018
Conclusions

• Overall, molecular taxonomy in bladder cancer shed light on the different biological processes underlying the tumorigenesis.

• Prospective studies are expected to “stabilize” the taxonomy and delineate how this taxonomy should be integrated in pathological practice.
Thanks !